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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,106	02/02/2001	Dcarg S Brown	PM-276502/Z-	8384

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/25/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,106	BROWN ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,9,10,12 and 13* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an RCE filed on 6/25/03. There are ten claims pending and ten under consideration. Applicants' amendment of 5/30/03 has been entered. Applicants amended claim 12. Claim 13 is new. All pending claims were previously rejected. Claims 1-3, 5, 6, and 8 are compound claims. Claim 10 is a composition claim. Claims 12 and 13 are use claims. Claim 9 is a synthesis claim. This is the third action on the merits. The application concerns some amidobenzamide compounds, compositions, and uses thereof.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/30/03 has been entered.

Claim Rejections - 35 USC § 112

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-3, 5, 6, 9, 10, and 12 remain rejected and claim 13 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "*in-vivo* cleavable

ester" in claims 1, 6, 10, and 12 is indefinite. The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "*in-vivo* cleavable ester" are molecules whose structure lie outside the subject matter of Formula I, but upon metabolism in the body are converted to active compounds falling within the structural scope of Formula I. The phrase describes the function intended but provides no specific structural guidance to what constitutes an "*in-vivo* cleavable ester". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 1. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise. Lines 4-13, page 23 list suitable esters, but use open language "for example". The Examiner suggests adding these specific examples to the claim to clarify what Applicants intend.

4. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim provide for the use of the compounds of formula I, but the claims do not set forth any steps involved in determining what is "a disease or medical condition mediated by TNF". It is unclear what diseases and treatments applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps

delimiting how to practice this use. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Lines 15-17, page 1 and 17-23, page 2 list some diseases Applicants regard as TNF related. The lists use open language, so what else is covered by the claim? Black (Ann. Reports Med. Chem.) considers cachexia, sepsis, Crohn's, encephalomyelitis, endotoxemia, and bone resorption as such diseases. Applicants do not list them. Are they covered by the claim or not? Black (Ann. Reports Med. Chem.) hints that all autoimmune diseases are so related. Should an enablement rejection be made over autoimmune diseases even though Applicants does not list them in his specification?

5. Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim provide for the use of the compounds of formula I, but the claims do not set forth any steps involved in determining what is "a disease or medical condition mediated by IL-1, IL-6 or IL-8". It is unclear what diseases and treatments applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps

delimiting how to practice this use. Identifying which diseases applicants intend this claim to cover will involve extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases applicants intend to treat, one skilled in the art cannot determine the metes and bounds of the claim. Applicants in lines 8-11, page 50 state their intention to inhibit such cytokines without stating which diseases are to be treated. Lines 15-17, page 1 and 17-23, page 2 discuss IL-1 but are silent as to IL-6 and IL-8. Fogarasi(Orv Hetil.) considers hepatic diseases, non-specific inflammatory bowel diseases (Crohn's disease and ulcerative colitis) and certain autoimmune diseases to be IL-6 related. Yet, Barton (Clin Immunol Immunopathol.) considers acute inflammation, such as toxic or septic shock, cachexia, multiple myeloma, and osteoporosis to be IL-6 related. These are totally different sets of diseases. Thus, there is confusion in the scientific literature as to which diseases fall into Applicants' claim limiatation. None of the diseases listed above are listed in the specification by Applicants as IL-6 related.

6. Claims 1-3, 5, 6, 9, 10, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the *in vivo* cleavable esters listed in lines 4-13, page 23, does not reasonably provide enablement for making all *in vivo* cleavable esters. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Synthesis of any particular *in vivo* cleavable ester would require identification of which esters are *in vivo* cleavable and devising a new synthesis of each ester. Considering the difficulty of the first step this is a large degree of experimentation. b) The direction concerning the *in vivo* cleavable esters was discussed above. There is no direction as to how to prepare these compounds. c) There is no working example of the identification of any *in vivo* cleavable esters let alone the synthesis of it. d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art with *in vivo* cleavable esters is that it is unknown which ester of which substrate fits the claim limitation. An acetoxymethyl ester of one substrate, which is in vivo cleavable, would not necessarily be so cleavable when applied to a different substrate. f) The artisan

using Applicants invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the millions of compounds of claim 1 as well as the presently unknown list of esters embraced by the phrase *in vivo* cleavable.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

7. Claims 12 and 13 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating rheumatoid arthritis and psoriasis, does not reasonably provide enablement for treating all TNF, Il-1, IL-6, or IL-8 mediated diseases. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have

been summarized above. a) Determining if any particular claimed compound would treat any particular TNF, Il-1, IL-6, or IL-8 mediated diseases disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different TNF, Il-1, IL-6, or IL-8 mediated diseases described above, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation.

b) The direction concerning treating TNF, Il-1, IL-6, or IL-8 mediated diseases is found in the lines 15-17, page 1 and 17-23, page 2, which merely states Applicants' intention to do so. Applicants describe formulations in lines 3-18, page 48. Doses required to practice their invention are described in the passage spanning line 19, page 48 to line 6, page 49. A 1,000-fold range of doses is recommended. Since no p38 inhibitor has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are three *in vitro*, one *ex vivo*, and one *in vivo* assay described in the passage spanning line 27, page 42 to line 7, page 47. There is data in only two of the *in vitro* assays for five compounds. It is unclear if these assay are correlated to TNF, Il-1, IL-6, or IL-8 mediated diseases. The *in vivo* assay appears to be prophetic. c) There is no working example of treatment of any disease in man or animals. There are no working examples of formulations. d) The nature of the invention is clinical treatment of disease, which involves

physiological activity. e) The state of the clinical arts in p38 enzyme inhibitors, which is the postulated mechanism of action of Applicants compounds, is provided by English (Trends) in figure 1, page 42 who summarizes in which diseases clinical trials have started. Barton (Clin Immunol Immunopathol.) discusses "the possibility of IL-6 both as a therapeutic agent and as a target for antagonists". Clarifying that such use is not presently art-recognized. Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the millions of compounds of claim 1 as well as the hundred of diseases embraced by the term TNF, Il-1, IL-6, or IL-8 mediated. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Allowable Subject Matter

8. Claim 8 is objected to as being dependent upon a rejected base claim.

Conclusion

9. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
July 24, 2003